REMARKS

Claims 1-13, 16-28 and 31 stand rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The Examiner alleges that the specification fails to support the claimed agents which would be capable of modulating the activity of sphingosine kinase. Specifically, the Examiner alleges that the specification only provides support for the use of the agents N,N-dimethylsphingosine and DL-threo-dihydrosphingosine. This rejection is respectfully traversed.

Applicants note that the claims have been amended to more specifically focus on the downregulation of sphingosine kinase activity in order to downregulate neoplastic cell growth which results from oncogene activity. Reference to the notion of upregulating cell growth by inducting sphingosine kinase oncogenic activity has been removed at this stage, however, applicants maintain the right to pursue this claim scope in one or more deleted and this may be pursued in a divisional application.

As described in detail below, the specification provides an extensive and detailed discussion of the types of molecules which one might utilize to downregulate sphingosine kinase functionality.

Sphingosine kinase, being the molecule which is the subject of downregulation herein, is not a novel protein. Rather, sphingosine kinase is a well known protein, which is encoded by an extensively characterized gene. Accordingly, the claims are not directed to the identification of modulatory agents based on generalized screening methodology which is designed in the context of an entirely novel gene or protein expression product. Rather, the claims are directed to the identification and use of agents which modulate the level of activity of a molecule which has been extensively characterized at both the structural and functional levels and in the context of the signaling pathway within which it functions. In this regard, agents which downregulate sphingosine kinase activity, and classes of agents in this regard, are well known and have been extensively described in the art. Those which are not yet known could be identified, without undue experimentation, as detailed above and as admitted by the Examiner.

The specification also provides detailed non-limiting exemplification in this regard in that it directs the person of skill in the art to the following agents or classes of agents which may be suitable for use in the method of the present invention:

Agents which modulate the expression of sphingosine kinase DNA or RNA including antisense RNA, ribosomes, DNAenzymes, microRNAs and molecules suitable for use in cosuppression.

Antagonists of the sphingosine kinase expression product, including antibodies, nucleic acid aptamers (page 20) and dominant negative sphingosine kinase variants.

Agents which modulate the catalytic activity of sphingosine kinase by competing with its substrate, these substrates including sphingosine kinase and ATP, for example. Still further exemplification is provided in the context of N,N-dimethylsphingosine and DL-threo-dihydrosphingosine (page 21, lines 15-16 and page 20, lines 18-19).

Agents which interfere with the catalytic activity of sphingosine kinase via an allosteric mechanism (page 21, lines 18-20).

Agents which interfere with sphingosine kinase enzyme activiation such as those which modify phosphorylation or lipid composition (these pathways being well characterized and defined), those which are coupled in a non-covalent manner to a required co-activator of the enzyme or those which modulate the subcellular localization of the enzyme (page 21, lines 21-28).

The identification and description of these classes of agents has been facilitated by virtue of the well characterized nature of sphingosine kinase. Accordingly, the person of skill in the art is provided with a disclosure in relation to both specific agents and classes of agents which would achieve the object of the invention and, together with the teaching provided in the specification, means of routinely screening for agents falling both within these defined classes and outside these classes. In this regard, the specification provides both a general description of the screening methodology which would achieve the object of identifying relevant agents (page 19, line 21-24 and page 36, line 1- page 37, line 24) and exemplified assays (Examples 1-3).

Accordingly the application, which identifies specific modulatory agents/classes of agents and describes means of screening for modulatory agents on a trial and error basis, does not place on the skilled person any undue burden of experimentation. In support of this position, we reiterate the there exists a highly relevant difference between the notion of screening for agents which modulate the activity of an entirely new protein or gene, which by definition will not have undergone extensive analysis over a prolonged period by those working in the field, versus the selection of a known modulatory agent or the identification of a modulatory agent in the context of a known and well defined molecule which has been extensively analyzed in terms of both its structure and function. In this regard, the analysis of sphingosine kinase has occurred not only in the context of sphingosine kinase *per se*, but in the context of its role as a component of a signaling pathway and its relationship to both upstream and downstream signaling molecules.

Still further, this application does not just provide a description of the desired function of the modulatory agent. Rather, the specification identifies specific agents exhibiting the desired characteristics of a modulator of sphingosine kinase activity and, further identifies examples of classes of agents which one might utilize. These classes have been described based on what is known in the art in relation to the functioning of the sphingosine kinase molecule. For example, prior knowledge of sphingosine kinase substrates and, thereby, the identification of antagonists which function by competing with these substrates has been facilitated as has the identification of agents which interfere with the activity of sphingosine kinase via allosteric mechanisms or which achieve interference of the enzymatic activity of sphingosine kinase by modifying phosphorylation or lipid compositions, which are important structural features of an enzyme which enable its functionality. Similarly, interference with the non-covalent coupling of the enzyme to a required co-activator is also a well known manner of downregulating enzymatic activity, these means being applicable in the present situation due to the extensive knowledge in relation to the structure and function of sphingosine kinase.

Therefore, the specification provides written description of the claimed subject matter.

The person of skill in the art has been directed to the nature of the agents which would be suitable for use in the invention and, further, to a means for identifying such agents, based not just on mere trial and error but on both the more detailed teachings contained in the specification in relation to sphingosine kinase structure and function and on that which is well known in relation to this extensively characterized molecule. In this regard, the fact that such modulatory agents exist and are known or can be routinely identified is demonstrated in the specification in the context of sphingosine kinase substrate competitors. The experimental evidence provided in the specification still further indicates that decreasing the levels of activity of sphingosine kinase can be actually achieved.

Claims 16-31 and 36-37 stand rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner states that the specification as originally filed fails to provide adequate written description fro the genus of conditions characterized by aberrant, unwanted or otherwise inappropriate cell growth. This claim language has been removed from the claims. Accordingly, this rejection should be withdrawn.

Claims 1-31 and 36-37 stand rejected under 35 USC 112, first paragraph, as not being enabled. Specifically, the Examiner alleges that the application only provides enablement for reducing the concentration of Ras-transformed fibroblasts by downregulating the activity of SphK using dimethylsphingosine or reducing the proliferation of human breast adenocarinoma cells by downregulating the expression of SphK using dimethylsphingosine but does not provide enablement for other cell types. The Examiner also alleges that the specification does not reasonably provide enablement for the treatment or prophylaxis of any condition, such as any malignant neoplasm, characterized by aberrant, unwanted or otherwise inappropriate cell growth. This rejection is respectfully traversed.

As a preliminary matter, the claims have again been amended to claim the downregulation of oncogene induced neoplastic cell proliferation and, further, the treatment of neoplastic conditions based on downregulating oncogene induced neoplastic cell proliferation.

In terms of the state of the art, the Examiner cites a seven year old textbook which states that there is no known anticancer agent or combination of anticancer agents that is effective against treating all cancer types. For example, the reference refers to the fact that there is no one chemotherapeutic agent which is effective in treating all cancers. Firstly, applicants question the relevance of a seven year old textbook, particularly since textbooks are themselves known to often be significantly out of date. Secondly, the present specification is directed to the treatment of neoplastic cells which have been rendered neoplastic by virtue of the upregulation of an oncogene. Still further, applicants question how an out of date text could be used to suggest that the present invention cannot support an important finding in relation to neoplastic cells, being that in the context of oncogene induced neoplasms, the downregulation of sphingosine kinase is effective in reducing proliferation.

Interestingly, this argument is in complete contrast to the citation and arguments raised by the Examiner in the context of anticipation and obviousness, where the Examiner argues that the present invention is not patentable in relation to any neoplastic cell on the basis that RAS oncogenic activity was so well known as a robust and most frequently activated oncogene in all forms of cancers. Accordingly, applicants are confused as to what the Examiner's position is on the state of the art.

In light of the teachings in the specification there is no reason why the skilled person would not accept that the finding of the oncogenic activity of sphingosine kinase does not represent a significant step forward in terms of the treatment of neoplasms. To this end, we also draw the Examiner's attention to the fact that the specification is not limited only to treatments which prevent cell growth but, further, treatments which at least downregulate or reduce cell growth.

We also point out that the cell model which has been used in the present application is one which has been induced by virtue of the transformation of a cell by the activated form of the RAS oncogene. This has been shown to confer a stable tumorogenic phenotype to most established cell lines and is a well known *in vitro* model by which oncogenic functionality can be

assayed. This position is, in fact, consistent with the arguments which the Examiner tries to make in the context of novelty. We also note that the MPEP suggest that an *in vitro* model example can constitute a working example if that example correlates with a disclosed or claimed method invention. We would suggest that such a correlation exists in the present case, particularly in light of the fact that this is a well recognized and accepted *in vitro* model of neoplasia, and that it therefore correlates to mammalian neoplastic conditions.

Claims 1-31 and 36-37 stand rejected under 35 USC 112, second paragraph, as being indefinite. The claim amendments remove the Examiner's issues. Accordingly, this rejection should be withdrawn.

Claims 1-10, 13-25, 28-31, 36 and 37 stand rejected under 35 USC 102(b) as being anticipated by Spiegel. This rejection is respectfully traversed.

As discussed above, the claims have now been amended to be limited to the downregulation of the proliferation of a neoplastic cell, where that neoplastic cell has become transformed due to the upregulation of an oncogene. These features were previously recited in claim 11. Since claim 11 was not rejected as being anticipated by Spiegel, this rejection should be withdrawn.

Claims 1-31, 36 and 37 stand rejected under 35 USC 103(a) as being unpatentable over Spiegel in view of Prashad. This rejection is respectfully traversed.

Spiegel discloses the identification and isolation of sphingosine kinase. Also disclosed are general methods of using the sphingosine kinase molecule in its known capacity to modulate various aspects of largely *normal* cellular functioning including the regulation of cell growth. Please note that the intracellular mechanisms which lead to hyperproliferation, i.e. increased cell growth, are completely distinct to the aberrant mechanisms which result in the transformation of a cell to a neoplastic cell.

The Examiner points out that Speigel does mention at page 36 of the specification the notion of treating cancer by administering an inhibitor of sphingosine kinase. As the Federal Circuit has stated a patent claim "cannot be anticipated by a prior art reference if the allegedly

anticipatory disclosures cited as prior art are not enabled." *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003).

Speigel's disclosure is not enabling for the purposes of anticipation on the basis that the specification provides absolutely no teaching or support in relation to the notion of sphingosine kinase functionality in the context of oncogenic neoplastic cells. Rather, the only example provided in the specification relates to hyperproliferative conditions, this being a completely distinct cellular proliferation mechanism to that which occurs in the context of a neoplastic state. Specifically, hyperplasias are the result of a stimulus which, upon its removal, results in the proliferation rate returning to normal. Accordingly, it effectively reflects an increased rate of proliferation of normal cells, as is observed in wound healing, mechanical stress and hormonal overproduction. However, neoplastic proliferation is an entirely distinct class of proliferation which continues in the absence of a stimulus.

The Examiner also alleges that the difference between Speigel and the present application is that Speigel fails to teach that the malignant neoplastic cell has been transformed due to upregulation of the oncogene RAS. Applicants reiterate that Speigel does not teach neoplastic cells but, rather, teaches hyperproliferative cells. The mention of neoplastic cells at page 36 of the specification is not supported by any teaching in the specification and the example in relation to hyperplasia cannot teach neoplasias, which are an entirely separate and distinct cell type which do require a stimulus to maintain cell proliferation, unlike hyperproliferative cells which do require the presence of an ongoing stimulus.

Applicants also wish to point out that the present invention is not limited to the downregulation of proliferation of cells in which RAS is functioning as an oncogene. This is merely an example, and support for claims directed to the downregulation of cells in which neoplasia has been induced by the activity of any oncogene. To this end, applicants have determined that even in the context of the presence of other oncogenes, sphingosine kinase itself nevertheless exhibits an increased activity and that its oncogenic activity, either together with another oncogene or in isolation, provides an appropriate target for treatment.

The Examiner is impermissibly using hindsight to link the identification of the role of sphingosine kinase in normal cells to its oncogenic potential. The Examiner does not appear to appreciate the extent of the difference between normal cellular proliferation and neoplastic cellular proliferation. Specifically, the mechanism by which a neoplastic cell is facilitated to proliferate in an uncontrolled manner is completely distinct to the proliferation mechanism of a normal cell. It is for this very reason that the normal physiological mechanisms by which proliferation of a normal cell is controlled cannot successfully control the aberrant and uncontrolled proliferation which is exhibited by a neoplastic cell. Accordingly, the uses and methods which are claimed in the current application do not relate to the identification of the mechanism by which a known compound achieves a previously known and disclosed result. Rather, the known compounds which are disclosed in the specification have surprisingly been determined to successfully control a significantly different final outcome, being the downregulation of the intracellular mechanism involved in the oncogene induced uncontrolled proliferation of a neoplastic cell rather than the normal proliferation mechanism of a non-neoplastic cell, such as a normal cell or a hyperproliferative cell. Finally, applicants note that Prashad neither discloses nor suggests that sphingosine kinase plays a role in oncogenic transformation or can itself function as an oncogene.

The Examiner has provisionally rejected claims 1-4, 6-19, 21 and 22 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8, 9, 11-15, 29, 49-55 of copending U.S. Patent Application No. 10/275,686. The Examiner has also provisionally rejected claims 1, 3-6, 16-18, 21, 22, 21, 36 and 37 under the judicially created doctrine of obviousness-type double patenting in view of claims 1-5, 7 and 18-26 of copending Application No. 10/531,626. Applicants acknowledge these provisional rejections, however, since these applications have not been allowed, no action is required at this time.

In the event that the transmittal letter is separated from this document and the Patent and Trademark Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **229752002600**.

Respectfully submitted,

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